not reduce DAF-16 levels or nuclear localization and still reduced lifespan in worms expressing a constitutively nuclear form of DAF-16. Nevertheless, depletion of two SCF E3 ligase F-box components (LIN-23 and PHI-3) did prevent the increased expression of genes activated by DAF-16, suggesting that they target cofactors that affect the ability of DAF-16 to activate longevity-promoting genes.

The results from Li *et al.* [6] and Ghazi *et al.* [7] show that ubiquitin-mediated proteolytic regulation targets both DAF-16/FOXO to limit lifespan and additional factors to extend lifespan. Moreover, it was recently shown that inactivation of a *C. elegans* F-box protein called DRE-1 results in the precocious expression of some cell fates expressed during larval development [15]. Larval transitions in *C. elegans* are temporally regulated and reminiscent of aging but occur earlier in life. Intriguingly, CUL-1 in vertebrates targets FOXO family members for degradation [16], and it will of course be interesting to learn whether ubiquitin-mediated proteolysis influences lifespan and aging in other animals.

In closing, the regulation of longevity is complex and multifaceted, and much remains unknown [4]. For example, reducing IIS doubles lifespan, while removing the germline in *C. elegans* IIS mutants results in a remarkable sixfold increase in lifespan [17]. In addition, mitochondrial function influences longevity, and the NAD-dependent histone deacetylase Sir2 also extends lifespan [4]. Each animal genome includes hundreds of genes that encode the machinery of proteolysis; exactly how many of them regulate lifespan remains to be seen.

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Institute of Molecular Biology, 1370 Franklin Boulevard, University of Oregon, Eugene, Oregon 97403, USA.
E-mail: bbowerman@molbio.uoregon.edu

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Host Genetics: Fine-Tuning Innate Signaling

A polymorphism modulating innate immunity signal transduction has recently been shown to influence human susceptibility to many different infections, providing one more indication of the potential of host genetics to reveal physiological pathways and mechanisms that influence resistance to infectious diseases.

Jacques Fellay and David B. Goldstein

A striking feature of all known infectious diseases is that no matter how devastating they may be there is always variation among humans in their susceptibility. In the middle of the 14th century, some people inexplicably survived Black Death while their entire villages were devastated [1]; in African cities with a high prevalence of HIV/AIDS, certain prostitutes remain uninfected after years of unprotected sexual contact [2]; more prosaically, some of us seem resistant to the flu virus without ever having had a vaccination.

A few of the underlying genetic causes for this variation have been shown to affect elements of both innate and adaptive immunity. Recent work has now established solid evidence for two hypotheses long suspected but as yet with little empirical evidence: first, that there are intermediate levels of immune response that are optimal, and second, that some genetic differences confer advantages against a broad range of infectious agents [3].

The strength of Darwinian selection associated with infectious disease is distressingly clear. The Black Death, again, is estimated to have killed between a third and two-thirds of Europe's population in 3 years (1348–1350), with a total number of victims probably reaching 75 million [1]; the influenza epidemic of 1918 killed between 50 and 100 million people worldwide (2.5–5% of the human population at the time) [4]. Clearly these diseases (and untold others not recorded by history) have molded patterns of human genetic variation. The search for signals of infection-driven selection in the human genome promise to shed new light on genes involved in crucial immunity pathways [5].

Classic examples of human polymorphism relate to infectious diseases. Erythrocyte polymorphic variants associated with protection against malaria have reached a state of balanced polymorphism, in which the deleterious consequences of the homozygous status are compensated, at the population level, by the protection conferred by the heterozygote status. Forerunner in this group, hemoglobin S, causing sickle cell anemia in homozygous individuals but highly protective against *Plasmodium falciparum* in heterozygous individuals, was identified more than half a century ago [6].

Even more noticeably, the major histocompatibility complex region (MHC), central to adaptive immunity, contains the most polymorphic set of genes identified in humans, but at the same time contains ancestral alleles that have been conserved for millions of years amongst different primate species [7]. This testifies to the very potent long-term action of balancing selection in the region, most probably maintained through pressure from infectious diseases.

In this context, it is somewhat surprising that, despite its long tradition of genetic studies, infectious disease genetics suddenly finds itself almost left behind. Proof-of-principle for the value of large-scale genetic studies is being established in various fields of biomedical research, with recent successes for example in metabolic [8] and inflammatory diseases [9]. However, as of this writing, there has still not been a single published whole-genome association study that has identified gene variants that influence host response to an infectious agent.

Yet another demonstration of the insights afforded by host genetics now comes from a recent candidate gene study of a component of the innate immunity signaling pathways. Khor *et al.* [3] describe a functional variant in a gene called Toll–interleukin 1 receptor domain-containing adaptor protein (TIRAP) that associates with protection against four widespread infectious diseases, which together constitute a major cause of mortality all over the world — invasive pneumococcal disease, bacteremia, malaria and tuberculosis.

At first glance, those diseases are dissimilar enough to make the finding of a common 'susceptibility gene' surprising. But the result is convincing, and the explanation is based on an essential characteristic of the innate immunity recognition system: the convergence of signaling pathways. Pattern recognition receptors, and notably Toll-like receptors (TLRs), are located at the interface between microbe and host and are therefore responsible for the first-line sensing of pathogens and for the crucial discrimination of non-self from self. After specific detection of evolutionarily conserved microbial structures, they differentially activate signal transduction pathways, leading to inflammatory and immune responses [10,11]. The key, it seems, is to achieve the appropriate level of immune response once foreign molecules are recognized.

Surface molecular structures from all sorts of bacteria (notably lipopolysaccharide and lipoteichoic acid), from mycobacteria (lipoarabinomannan) and also from *Plasmodium falciparum* (glycosylphosphatidylinositol) [12] are recognized by the TLR2 and/or the TLR4 receptors. Interacting with their intracellular domain, both receptors share a downstream adaptor protein, the MyD88 adapter-like protein (Mal), which is the product encoded by the TIRAP gene [13]. Placed at the crossroads between the first-line receptors and a restricted number of downstream convergent molecules, Mal is able to modulate the strength of the signal following activation.

The Mal variant identified in the new study [3] is an amino-acid substitution (leucine for serine at position 180, S180L). This rare allele associates with a decrease in signal-transduction efficiency and, in heterozygous form, is associated with protection against infectious agents [3]. In contrast, the very few patients that are homozygous for the S180L variant seem to be highly susceptible to the same pathogens, probably because of failure in specific immune signaling. This sort of genetic model would generally raise suspicions of a 'false-positive' association. In this case, however, the association results are unusually strong (indeed, the combined P-value would survive correction in the context of a genome-wide association study using tagging single nucleotide polymorphisms). The authors also provide a compelling explanation for the genotypic effects. As has been hypothesized many times, these results suggest that an intermediate state of activation of the signaling cascade is optimal to reconcile the goal of keeping the body alert to fight infection, while restraining the inflammatory response that can, itself, be harmful to the host. This proposal is consistent with 'heterozygote advantage': individuals homozygous for the rare variant mount too weak a response, while the heterozygote response is optimal [7].

The minor allele frequency of the Mal S180L variant is very low, except in patients of European ancestry (approximately 0.15 in Caucasians and 0.02 in Africans and Asians, which is concordant with frequencies observed in HapMap samples). Consequently, the fraction of global susceptibility to each infection explained by this

Table 1. Global mortality due to major infectious diseases.

Infectious diseases	Deaths in 2002	Percentage of all deaths
Lower respiratory infections	3.9 million	6.90%
HIV/AIDS	2.8 million	4.90%
Diarrheal diseases	1.8 million	3.20%
Tuberculosis	1.6 million	2.70%
Malaria	1.3 million	2.20%
Measles	0.6 million	1.10%
Pertussis	0.29 million	0.50%
Tetanus	0.21 million	0.40%
Meningitis	0.17 million	0.30%
Syphilis	0.16 million	0.30%

(Adapted from the WHO world report 2004.)

single polymorphism remains low, even though it is very significant in heterozygous individuals (up to 50% reduction in susceptibility to various major diseases). A low explained fraction is an argument in support of the idea that susceptibility to infectious diseases is highly polygenic: many loci with modest effects (on global susceptibility) are likely to be involved. The logical conclusion is that most of the inter-individual variability has still to be uncovered.

Human susceptibility or resistance to microbial attack can be seen as the final result of a dynamic interplay between the genetic make up of the individual host and the pathogen, with environmental influences adding another layer of complexity. In the middle of such an intricate picture, however, it is reassuring for host genetics research that some well-established examples of human polymorphisms clearly influence the outcome of various infections. These polymorphisms are located in genes that encode cellular co-factors directly implicated in the life cycle of pathogens (such as the chemokine receptor CCR5 [14]); proteins involved in innate recognition of microbes and first-line defense innate immunity pathways (such as the TLRs [15]); or molecules that regulate adaptive immune responses (most notably the HLA region bearing the MHC class I and II genes [16]). This functional distribution makes sense but is likely to be largely incomplete: the vast majority of variants have been found in candidate gene studies, which can only test *a priori* hypotheses, and even these studies have generally been incomplete: despite its prominence, the HLA region is normally only studied at the level of allelic diversity represented by classical HLA typing. Causal variants in the region, such as those influencing expression, would be missed.

Infectious diseases remain major killers today, especially in less-developed countries (Table 1). The fight against mortality and morbidity due to common pathogens has, by nature, to be global, and certainly warrants a much more dedicated effort from the scientific community. As we enter a new era of genomic knowledge and technological potential, there is a new hope that large-scale association studies will reveal important human genetic components that could be targeted by drugs or vaccines. It is time to carry out comprehensive large-scale host genomic analyses of all the major infectious agents. Together these pathogens are responsible for more than 10 million deaths per year. Results such as those from Khor *et al.* [3] make clear the importance of host genetics. There is reason to be optimistic that genome-wide association studies will prove a key tool in the global effort to reduce the morbidity and mortality caused by these diseases.

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Center for Population Genomics & Pharmacogenetics, Duke Institute for Genome Sciences and Policy, Duke University, Durham, North Carolina 27710, USA.
E-mail: jcf20@duke.edu

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